



Crosstalk between Endoplasmic Reticulum Stress, Unfolded Protein Response (UPR) and Wnt Signaling Pathway in Cancer

Morvarid Siri¹, Seyed Vahid Hosseini², Sanaz Dastghaib¹, Pooneh Mokarram^{3*} 

¹Department of Biochemistry, Shiraz University of medical sciences, Shiraz, Iran

²Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

³Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

*Corresponding authors:

Pooneh Mokarram, Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Email: mokaram2@gmail.com

Received: 16-02-2020

Revised: 16-02-2020

Accepted: 16-02-2020

Abstract

Context: Endoplasmic reticulum stress (ER stress) is associated with endoplasmic reticulum perturbation homeostasis. Prolonged ER stress conditions may induce cell death. Unfolded protein response (UPR) attempts to restore normal cell conditions.

Evidence Acquisition: There now exists an emergent body of evidence identifying the WNT signaling network as a regulator of cancer cell metabolism. Given that existing findings show that the WNT pathway and ER stress regulates changes in metabolic activities of cancer cells suggesting these signaling pathways represent critical nodes in the regulation of central metabolism in tumors.

Results: Findings suggest that the molecular cross-talks between hypoxic ER stresses, Wnt/ β catenin signaling, may represent an important mechanism that enables some tumor subtypes to survival and grow in hypoxic conditions.

Conclusions: The present article disuses differential effects of the activation of the three arms of UPR, namely endoplasmic reticulum kinase (PERK), activation transcription factor -6 (ATF-6), and inositol γ -requiring enzyme (IRE-1) on cancer. This review also highlights regulators and downstream effectors of Wnt cascade and addresses the increasingly apparent crosstalk of Wnt with other tumorigenic signaling pathways.

Keywords: Endoplasmic reticulum, Stress, Cancer, UPR, Wnt

Please cite this paper as:

Siri M, Hosseini SV, Dastghaib S, Mokarram P. Crosstalk between Endoplasmic Reticulum Stress, Unfolded Protein Response (UPR) and Wnt Signaling Pathway in Cancer. *Ann Colorectal Res.* 2020;8(1):9-16. doi: 10.30476/ACRR.2020.46538.

Context

The unfolded protein response (UPR) is a cellular stress response that works with the Wnt signaling pathway; activation of these cascades can trigger tumorigenesis.

Evidence Acquisition

Due to the Wnt pathway components and UPR crosstalk, targeting of Wnt signaling could affect tumor progression. A study carried out by Pyrko P et al. (2007) showed that an inhibitor of UPR, epigallocatechin gallate (EGCG; a tea catechin), blocks the ATP-binding domain of glucose-regulated protein and sensitizes cells to the first-line drug, temozolomide (TMZ) (1).

Moreover, CK2 inhibition by Silmitasertib (CX-4945) potently downregulates UPR signaling by downregulating GRP78/BIP, a marker of UPR activation (2). β -catenin is accumulated by Enzastaurin, a bisindolylmaleimide derivative. UPR-mediated growth is arrested, and c-Jun-mediated apoptosis is triggered (3).

Results

1. Unfolded Protein Response (UPR) Signaling Pathway

The endoplasmic reticulum is involved in such cellular processes as protein folding, post-translational modifications, and protein translocation, with a capacity for protein folding related to the expression level of *glucose-regulated proteins (GRPs)*, namely GRP78, GRP94 and GRP18.

When the cells of the body are damaged for any reason, all signaling pathways and compensatory mechanisms are activated in organelles to restore intracellular homeostasis and create an adaptive defense system. In this study, our focus is on a condition called endoplasmic reticulum stress. In a general sense, stress refers to conditions where there is so much pressure in a system that it disrupts its balance and performance. As such, endoplasmic reticulum stress is a condition in which the amount of cellular demand exceeds the coping capacity of the endoplasmic reticulum (4-7).

There are various direct or indirect biochemical, physiological, and pathologic stress-causing factors that cause oscillations and interfere with the endoplasmic reticulum, namely hypoxia, glucose shortage, metabolic inhibitors, calcium pumps, glucose inhibitors, various reviving factors, and viral infections. When poorly folded proteins are accumulated, they trigger several defense mechanisms (8-10). Unfolded protein response (UPR) is signaling pathway affected by pancreatic endoplasmic reticulum kinase (PERK), activation transcription factor-6 (ATF-6), and inositol-requiring enzyme 1 (IRE-1) (Figure 1). Located on the endoplasmic

reticulum, the aforementioned sensors serve as the key arms in triggering the pathway for the UPR (11-13). The activation of signaling pathways reduces the synthesis of misfolded proteins by suppressing the synthesis of new proteins and by increasing the capacity for protein folding.

The arms in this pathway should not be seen as distinct signaling pathways. Rather, they form a network with a strong association with other intracellular pathways such as autophagy and cell death. The relationship between this pathway and other stress response pathways can ultimately determine the fate of the stress-induced cell.

Unfolded protein response is a highly evolutionary process associated with stress induction in protein folding under pathological and physiological conditions. The components of this signaling pathway regulate inflammation, lipid / cholesterol metabolism, energy homeostasis, and cell differentiation (14, 15).

1.2. Glucose Regulated Protein 78 (GRP78)

Glucose regulated protein 78 (GRP78) is a heat shock protein (HSP) located in the endoplasmic reticulum. It exists in a range of organisms from yeast to human. Furthermore, it is responsible for several important intracellular processes, including the facilitation of the transfer, completion and accumulation of newly produced proteins in the cell, and prevention of the accumulation of misfolded proteins (13, 16).

This protein is a key factor in controlling and activating signaling pathways. It binds itself to the components of the signaling pathways, thereby suppressing their function. In general, as a sensor and regulator, it identifies endoplasmic reticulum stress. As misfolded proteins are accumulated, GRP78 is removed from sensors present on the endoplasmic reticulum membrane. Furthermore, it initiates UPR pathways within the cell. In fact, recent studies suggests that activated transcription and nuclear factors down this pathway affect the expression of more than 1700 genes within the cell (17, 18).

Recent research has confirmed the presence of this sensor in such parts of the cell as the cytoplasm, mitochondria, nucleus and plasma membrane. Under stress conditions of the endoplasmic reticulum, the uptake of GRP78 into the mitochondria increases. Thanks to its role in maintaining the integrity of the mitochondrial membrane, it protects the organism from apoptosis induced by endoplasmic reticulum stress (11, 12, 19).

1.3. Pancreatic Endoplasmic Reticulum Kinase (PERK)

The serine / threonine transporter membrane protein kinase is located on the endoplasmic reticulum; under normal cellular conditions it is a passive monomer with physical binding to GRP78. When the endoplasmic reticulum becomes stressed,

the glucose-regulated protein is removed by PERK. Hence, it is oligomerized and activated. Once PERK is activated, it initiates signaling pathways that trigger the transcription of certain genes in the cellular nucleus. The most important substrates of this sensor are eukaryotic initiation factor 2 α (eIF2 α) and nuclear factor E-2-related factor 2 (Nrf2) (20, 21).

Activating this sensor triggers the phosphorylation of the eukaryotic translation initiation factor 2, which, in turn, results in reduced mRNA translation initiation of a number of proteins. Activated eukaryotic translation initiation factor 2 also enhances the translation of a number of genes for the signaling pathway of unfolded proteins, including activated transcription factor 4 (ATF-4). The expression of pre-apoptotic proteins under prolonged stress conditions induces cell death. Therefore, in addition to helping cells survive, PERK can also trigger cell death under stressful conditions of the endoplasmic reticulum. Recent studies show that PERK inhibits cell growth by influencing cyclin D1 at the G1 stage of the cell cycle during endoplasmic reticulum stress (22-24).

1.4. Inositol-requiring enzyme (IRE-1)

A type 1 transaminase protein with dual enzymatic activity in the cytosolic region includes serine / threonine kinase and ribo endonuclease, which is autophosphorylated and oligomerized in response to endoplasmic reticulum stress. The mammalian genome encodes alpha and beta genes of this sensor. The alpha type is expressed in the cells of most tissues, whereas the beta type is found only in the lung and intestinal epithelial cells as well as the mucosal epithelial tissues. Among the signaling pathways for UPR, the alpha type is a key sensor, which is able to regulate the cell's pathway to death or survival (18, 25).

The inositol-requiring enzyme alpha type provides the active form of the X-box-binding protein (XBP1) mRNA transcription factor. The activated and spliced variant of this factor increases the capacity of the involved organelles for protein folding by modulating the expression of genes involved in proper unfolding of proteins, secretion and destruction of endoplasmic reticulum proteins.

If the attempt to restore endoplasmic reticulum homeostasis fails, the inositol-requiring enzyme discontinues splicing the XBP1. In addition, it reduces the endoplasmic reticulum proteins by influencing the nuclear factor-c-Jun NH2-terminal kinase (JNK), NF κ B, and inositol-requiring enzyme decay RIDD (IRE-1 dependent decay), with the ability to decrease the expression of some mRNAs and microRNAs (26, 27).

It seems that endoplasmic reticulum stress increases during the transition from an enzyme-dependent adaptation response of IRE-1 to the initiation of the cell death pathway under prolonged endoplasmic reticulum stress. This increase is due to the enzyme-

dependent degradation process of inositol-requiring enzymes, wherein target genes that signal pathway of unfolded proteins such as GRP78 are degraded. Therefore, prolonged endoplasmic reticulum stress triggers induction of cell death (28, 29).

1.5. Activating Transcription Factor 6 (ATF6)

A type 2 trans-membrane protein with the N-terminal cytoplasmic domain containing a DNA-binding motif and a C-terminal domain within the lumen of the endoplasmic reticulum, which binds itself to GRP78. The expression of ATF6 regulates protein-dependent pathway genes in endoplasmic reticulum associated protein degradation (ERAD). In mammals, there are two homologues of ATF6, namely alpha (90 KD) and beta (110 KD), both of which are synthesized within the endoplasmic reticulum and activated by endothelial network stress response via endothelial proteolysis (21, 30).

Endoplasmic reticulum stress drives alpha type ATF6 from the endoplasmic reticulum to Golgi network, where the proteolytic removal of alpha type ATF6 is carried out by Specificity Proteins SP1 and SP2 proteases. Here, a free membrane is released from the ATF to be transferred to the nucleus. As a result, the major genes involved in protein folding and the degradation of pathway of proteins in the endoplasmic reticulum are transcribed.

When precursor forms attached to the endoplasmic reticulum membrane are separated from the alpha and beta type ATF6 during endoplasmic reticulum stress, and their N-terminal ends become soluble transcription factors, the mentioned transcription factors are activated and regulate the expression of genes for the response pathway to unfolded proteins by directly binding to stress response elements of the endoplasmic reticulum in the target gene promoter (31-33).

2. The Dual Role of the Signaling Pathway in the Unfolded Proteins Response (UPR) in Cancer Progression

Endoplasmic reticulum activity increases as tumor cells grow and proliferate in order to accelerate the proper uptake of proteins and facilitate their intracellular transport. The consequences of this growth are hypoxia, starvation, oxidative stress, cellular calcium depletion, and ultimately endoplasmic reticulum stress and the initiation of the unfolded protein response (UPR) compensatory pathway. This pathway functions in opposite directions: on the one hand, it promotes normalization by stopping translation and protein synthesis and increasing the production of chaperones to correct folding of accumulated proteins; on the other hand, it initiates the cell death pathway from both mitochondrial-dependent and mitochondrial-independent mechanisms and ultimately activates the caspases within the cell (34, 35).

The UPR pathway is initiated as endoplasmic

reticulum associated protein degradation (ERAD) initiates the complete degradation of unfolded proteins by identifying and destroying them with the polyubiquitin in the proteasome through two processes, namely proteasomal degradation and autophagy. The post-stress activation of autophagy in the endoplasmic reticulum has two contradictory consequences, namely cell protection and cell death. The therapeutic goal is to drive this pathway to cell death by ensuring that the drug elicits an optimal response. Continuous stimulation and prolonged stress of the endoplasmic reticulum drive the autophagy pathway and shift the response pathway of unfolded proteins to apoptosis (15, 36).

The accumulation of unfolded proteins increases the expression of the primary chaperone in the endoplasmic reticulum, called GRP78, separating this protein from membrane sensors on the endoplasmic reticulum containing three specific proteins that serve as the major arms in initiating the response pathway:

1. IRE-1 Inositol requiring enzyme-1
2. ATF-6 Activating transcription factor-6
3. PERK Pancreatic endoplasmic reticulum kinase

After the separation of the GRP78, PERK, ATF-6 and IRE-1 are activated in order. The PERK factor phosphorylates the eukaryotic translation initiation factor 2, stopping the synthesis of some proteins. In addition, ATF6 is separated from the Golgi network by specificity proteins SP1 and SP2 proteases. Upon entering the nucleus, this factor translates various genes including PERK and chaperones such as X-box protein transcription factor, whose mRNA requires specific splicing within the cytoplasm via the dual activity of serine threonine kinase and endoribonucleoside enzyme transcription factor. PERK transcription factor has specific functions, namely activating eukaryotic translation initiation factor 2, stopping protein synthesis and activating CHOP protein (C/EBP homologous protein), which activates the cell death receptor 5 (DR5), inhibits cell growth, and initiates growth arrest and DNA damage 153 (GADD153). Thus, this process alters cell status from cell protection to pre-apoptotic cell death and initiates caspase cascade enzymes (37-39). In sum, the UPR pathway can be used as a therapeutic target. This pathway can exert both protective and destructive effects on cell survival in cancer cells.

Contrary to cancer cells, in most normal cells, the UPR pathway is not very active. This is considered an advantage in treatment because targeting this pathway can specifically affect the cancer cells (40). It was in 2004 that the role of the endoplasmic reticulum signaling pathway in cancer development was first proposed. Cancer progression is characteristically associated with uncontrolled growth, deformed cell proliferation, and lack of oxygen and glucose in the tumor environment. It is therefore not surprising that activation of the

UPR pathway represents a hallmark in regulating various human cancers. The activation of the UPR signaling pathway enables cancer cells to survive in adverse environmental conditions, thereby leading to resistance to chemotherapy drugs. The pathway also contributes to tumor-stimulated angiogenesis, especially in early cell proliferation when glucose and hypoxia deficiency can compromise tumor growth. The three different arms of the signaling pathway have different effects on the response of unfolded proteins to different types of tumors at different stages of tumor development, namely growth, proliferation and survival. For example, the enzyme transcription factor signaling pathway requires inositol during hepatocellular carcinoma initiation, whereas activation of the PERK transcription factor is required when the tumor is created. Therefore, it is used to maintain cell survival and causes therapeutic resistance (41, 42).

The contribution of the UPR signaling pathway to stress response in the endoplasmic reticulum is related to its adaptive function. It gives cancer cells the ability to cope with stress, thereby increasing their growth, proliferation, and drug resistance (43).

Endoplasmic reticulum stress may be manipulated to treat cancer stem cells as different unfolded protein signaling pathways are activated in these cell lines, helping cell survival against stress stimuli. Inhibition of three sensors along with pro-death factors can increase the sensitivity of these cells to treatment.

The unfolded protein signaling pathway and hypoxia can be independently stimulated by Vascular Endothelial Growth Factor (VEGFR) gene expression through PERK / ATF4 and HIF1 / 2 pathways (44).

The unfolded protein signaling pathway can be used as a pro-tumorigenic agent to increase the capacity of the UPR and induce resistance to anticancer drugs. The signaling pathway for the UPR can be used as an anticancer treatment strategy in two ways:

1. The UPR signaling pathway is blocked as a survival response.
2. Endoplasmic reticulum stress rises above the threshold in cells contingent on signaling UPR pathways to trigger cell death.

Resistance mechanisms to treatment may include decreased drug uptake, altered drug targeting, induction of drug detoxification mechanisms, repair of drug-induced damage, and insensitivity to drug-induced cell death (15, 34, 35, 45). Furthermore, hypoxia activates the inositol-requiring enzyme transcription factor as a survival signal in cancer cells.

The enzyme transcription factor of inositol-requiring enzyme and X-box-binding protein / signaling pathway of unfolded proteins help induce chemotherapy resistance. The PERK transcription factor signaling pathway helps cancer cells survive in response to hypoxic conditions and reactive oxygen species (ROS) (46-48). A number of studies have shown that the effect of GRP78 on drug resistance mainly involves a decrease in drug-

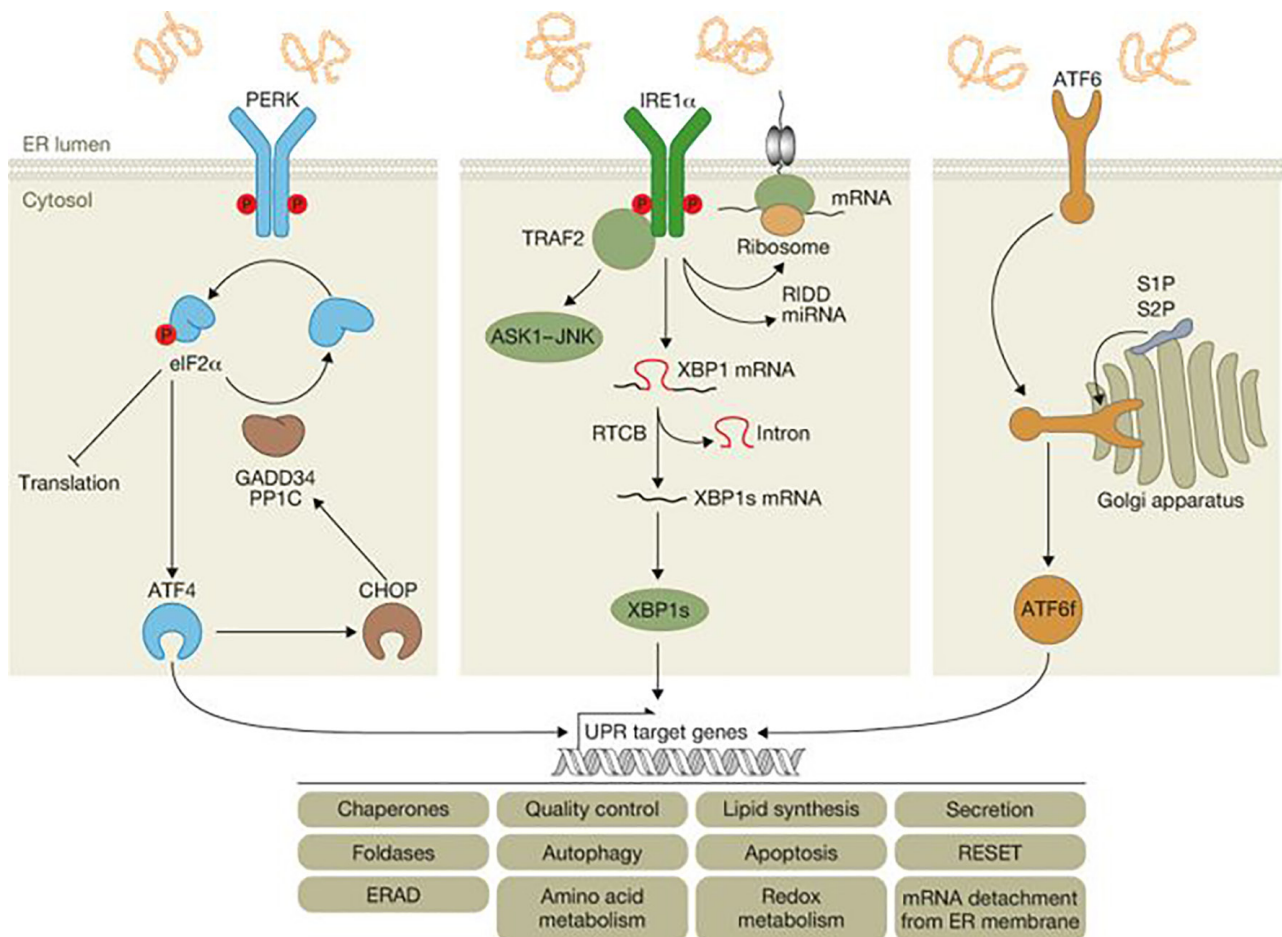


Figure 1: Unfolded protein response (UPR) signaling pathways (67). The UPR is controlled by three stress sensors on the endoplasmic reticulum membrane: Inositol-requiring enzyme (IRE-1), pancreatic endoplasmic reticulum kinase (PERK) and activation transcription factor 6 (ATF-6). The PERK phosphorylates the initial eukaryotic translation factor 2, suppresses protein translation, and activates activation transcription factor 4 (ATF-4). Activation transcription factor 4 (ATF-4) participates in biological processes as a transcriptional repressor and activator of multiple genes.

The IRE-1 activates X-box-binding protein (XBP1), thus affecting the processing of genes responsible for protein folding (ERAD; endoplasmic reticulum associated protein degradation) and secretory pathways. ATF-6 must be transferred to the Golgi to be activated by S1P and S2P proteases. ATF-6 fragments (50KD) are then transferred to the nucleus. The aforementioned pathways regulate chaperones and their corresponding specific targets to counteract endoplasmic reticulum stress and maintain homeostasis.

induced apoptosis. However, its precise molecular mechanisms have not been elucidated (49-53).

In severe hypoxia and chemotherapeutic conditions, when the signaling pathway of the UPR is activated, the expression of GRP78 increases in high esophageal cancer (hypopharyngeal carcinoma) along with resistance to hypoxia chemotherapy (54). Disruption of GRP78 in endothelial cells makes them susceptible to drug therapy, which opens many windows on the role of signaling pathway sensors in the UPR (55, 56). Glioma cells that are treated with an inhibitor of the signaling pathway responding to unfolded protein, epigallocatechin gallate (EGCG; a tea catechin), block the ATP-binding domain of glucose-regulated protein and sensitize cells to the first-line drug, temozolomide (TMZ)(1). A decrease in GRP78 inhibits cell proliferation and increases cisplatin-treated apoptosis in severe hypoxic conditions. This indicates that GRP78 inhibits cisplatin-resistant cancer cells (cisplatin) and regulates the response to severe hypoxia (54, 57).

3. Crosstalk between the UPR and the Wnt Pathway

When UPR is activated, some aspects of Wnt signaling are inhibited in a PERK-dependent manner. In *Caenorhabditis elegans*, endoplasmic reticulum stress decreases Wnt expression in a PERK-dependent manner. In neuronal diseases, both the activation of the UPR and loss of Wnt signaling have been implicated in neurodegeneration and the progression of Alzheimer's and Parkinson's diseases. It is therefore possible that inhibition of canonical Wnt signaling as a result of UPR activation could be a contributing factor (58).

β -Catenin is best known as a key signal transducer in the canonical WNT pathway, which is dysregulated in many cancers. Under physiologic conditions, stabilized β -catenin enhances proliferation and protects against apoptosis. Inhibiting phosphorylation of β -catenin by Enzastaurin, a bisindolylmaleimide derivative, helps β -catenin to accumulate and eventually triggers apoptosis via c-Jun-stabilized p73 (Figure 2) (3).

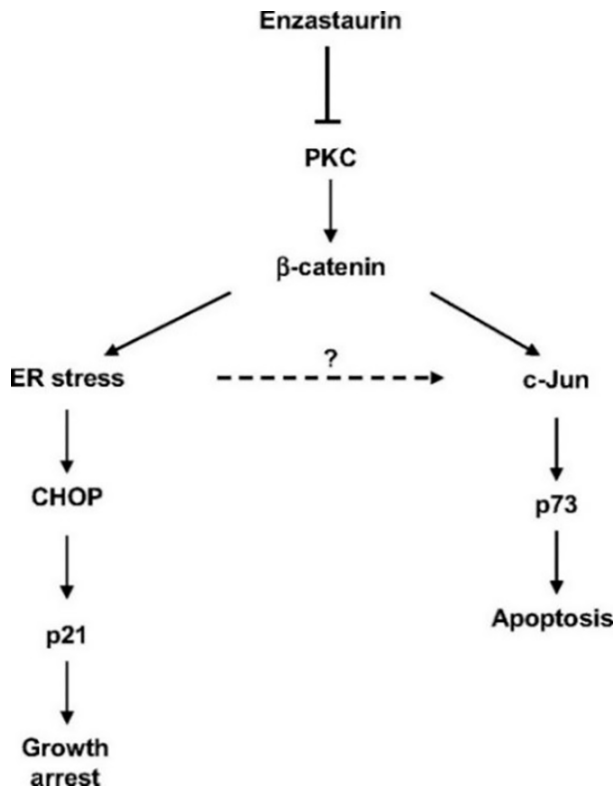


Figure 2: β -catenin is accumulated by Enzastaurin; UPR-mediated growth is arrested, and c-Jun-mediated apoptosis is triggered (3).

Recent evidence demonstrates that UPR helps the cell to overcome hypoxic stress (59) via HIF-1 and HIF-2. Meanwhile, Wnt/ β -catenin signaling can disrupt the co-operative activation by XBP1s-HIF1 α . Hypoxia inhibits β -catenin/TCF-4 formation in HCT116 and SW480 colon cancer cells with constitutively high levels of β -catenin, as β -catenin binds directly to HIF1 α . In contrast, in RKO colon cancer cells with normal Wnt/ β -catenin signaling capacity, hypoxia inhibits β -catenin accumulation, reduces LRP6 protein level, and impairs Wnt signaling transduction. Furthermore, Wnt stimulation or β -catenin overexpression has a small effect on the HIF1 α -regulated gene expression program in hypoxia. Furthermore, β -catenin diminishes the co-operative cross-talk between the HIF1 α and XBP1s pathways. In conclusion, the results suggest that hypoxia may influence Wnt/ β -catenin in a number of colon cancer types (60).

Furthermore, tumor stress often activates heat-shock proteins (HSPs) and the UPR as pro-survival mechanisms (61). A component of the transcriptional arm of the UPR, HSP90, triggers protein folding/unfolding. Furthermore, Casein kinase 1 (CK1), Casein kinase 2 (CK2), and GSK3 β , which play crucial roles in the Wnt pathway, help to regulate the Wnt pathway as well as HSP70 and HSP90 (62, 63). They also have an effect on HOP (HSP70-HSP90 organizing protein) and the chaperone-binding ubiquitin ligase (CHIP), and determine the cellular protein folding/degradation balance. Likewise, C-terminal phosphorylation regulates binding to

co-chaperones. The C-terminal phosphorylates HSP70 and HSP90, enhancing the assembly with HOP. The non-phosphorylated chaperones mediate the degradation of client proteins by preferring to bind to CHIP. CK1 and CK2 might be contributors to endoplasmic reticulum stress/UPR. When CK2 is inactivated, the expression levels of co-chaperone Bip/Grp78 and kinase/endoribonuclease IRE1 α decreases, but the PERK and eukaryotic initiation factor 2-eIF2 α are activated. In conclusion, a reduced synthesis of Bip/Grp78 messenger RNA (mRNA), and an increased expression of ATF6-dependent EDEM mRNA suggest a negative role of CK2 on the ATF6 branch of the UPR (64).

CK2 helps to control the UPR and regulate ER stress. CK2 and p38 MAP kinase directly interact in response to TNF α . Furthermore, TNF α activates UPR. In addition, p38 MAP kinase phosphorylates a spliced form of XBP-1 at the residues Thr48 and Ser61. Then, Thr48 and Ser61 enhance nuclear migration (65).

Moreover, CK2 inhibition (i) reduces the levels of the ER stress sensors IRE1 α and BIP/GRP78, (ii) increases phosphorylation of PERK and EIF2 α , and (iii) enhances ER stress-induced apoptosis. Simultaneous inactivation of CK2 and HSP90 results in a synergic anti-myeloma effect and in much stronger alterations of the UPR pathways as compared with the isolated inhibition of each of the two molecules (66). These results place CK2 as a novel regulator of the ER stress/UPR cascades and HSP90 function in myeloma cells. Furthermore, CK2 inhibition by Silitasertib (CX-4945) potently downregulates UPR signaling in T-cell acute lymphoblastic leukemia cell lines by downregulating GRP78/BIP, a marker of UPR activation (2).

Conclusions

Intracellular homeostasis may be maintained by processes involved in the endoplasmic reticulum stress pathway and the unfolded protein response (UPR) if proper therapeutic strategies are adopted. In the short run, stress induces cellular resistance through signaling pathway arms. In addition, the mentioned processes trigger adaptive and protective arms for cell survival. Nonetheless, in the long run, high-intensity stress triggers cell death. There is a widespread effort to manipulate the endoplasmic reticulum stress pathway and UPR in such way as to help cure various diseases including cancer. The UPR pathway can be manipulated in two ways: 1) inhibiting the growth and proliferation of cancer cells that use this pathway to survive in stressful situations 2) allowing it to accumulate as much misfolded and unfolded proteins in the cell as possible, and continuously activating the functional arms of the UPR pathway to trigger programmed cell death in the cancer cells.

Unlike in cancer cells, the pathway for the UPR is not

very active in normal cells; this fact is an advantage for cancer treatment as targeting regulatory molecules of this pathway can specifically affect the cancer cells and prevent their rapid growth. In addition, the molecular interface between Wnt/ β catenin signaling

and UPR enables some tumor types to survive in stress conditions. Thus, it is vital to find the best combination of strategies to inhibit tumor growth.

Conflict of Interests: None declared.

References

1. Pyrko P, Schönthal AH, Hofman FM, Chen TC, Lee AS. The unfolded protein response regulator GRP78/BiP as a novel target for increasing chemosensitivity in malignant gliomas. *Cancer research*. 2007;67(20):9809-16.
2. Buontempo F, Orsini E, Martins LR, Antunes I, Lonetti A, Chiarini F, et al. Cytotoxic activity of the casein kinase 2 inhibitor CX-4945 against T-cell acute lymphoblastic leukemia: targeting the unfolded protein response signaling. *Leukemia*. 2014;28(3):543-53.
3. Raab MS, Breikreutz I, Tonon G, Zhang J, Hayden PJ, Nguyen T, et al. Targeting PKC: a novel role for β -catenin in ER stress and apoptotic signaling. *Blood*. 2009;113(7):1513-21.
4. Ozgur R, Uzilday B, Iwata Y, Koizumi N, Turkan I. Interplay between unfolded protein response and reactive oxygen species: a dynamic duo. *Journal of experimental botany*. 2018;ery040.
5. Manalo RVM, Medina PMB. The endoplasmic reticulum stress response in disease pathogenesis and pathophysiology. *Egyptian Journal of Medical Human Genetics*. 2017.
6. Schröder M. Endoplasmic reticulum stress responses. *Cellular and molecular life sciences*. 2008;65(6):862-94.
7. Kapoor A, Sanyal AJ. Endoplasmic reticulum stress and the unfolded protein response. *Clinics in liver disease*. 2009;13(4):581-90.
8. Salminen A, Kaarniranta K. ER stress and hormetic regulation of the aging process. *Ageing research reviews*. 2010;9(3):211-7.
9. Kim I, Xu W, Reed JC. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nature reviews Drug discovery*. 2008;7(12):1013.
10. Kim SR, Lee YC. Endoplasmic reticulum stress and the related signaling networks in severe asthma. *Allergy, asthma & immunology research*. 2015;7(2):106-17.
11. Kelsen SG. The unfolded protein response in chronic obstructive pulmonary disease. *Annals of the American Thoracic Society*. 2016;13(Supplement 2):S138-S45.
12. Wang M, Wey S, Zhang Y, Ye R, Lee AS. Role of the unfolded protein response regulator GRP78/BiP in development, cancer, and neurological disorders. *Antioxidants & redox signaling*. 2009;11(9):2307-16.
13. Regulation H. The Unfolded Protein Response: From Stress Pathway to science. 2011;1209038(1081):334.
14. Lindholm D, Korhonen L, Eriksson O, Köks S. Recent insights into the role of unfolded protein response in ER stress in health and disease. *Frontiers in cell and developmental biology*. 2017;5:48.
15. Senft D, Ze'ev AR. UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. *Trends in biochemical sciences*. 2015;40(3):141-8.
16. Cybulsky AV. Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases. *Nature Reviews Nephrology*. 2017;13(11):681.
17. Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nature reviews Molecular cell biology*. 2007;8(7):519.
18. Doultanos D, Avril T, Lhomond S, Dejeans N, Guédal P, Chevet E. Control of the unfolded protein response in health and disease. *SLAS DISCOVERY: Advancing Life Sciences R&D*. 2017;22(7):787-800.
19. Gopal U, Pizzo SV. The Endoplasmic Reticulum Chaperone GRP78 Also Functions as a Cell Surface Signaling Receptor. *Cell Surface GRP78, a New Paradigm in Signal Transduction Biology*: Elsevier; 2018. p. 9-40.
20. Corazzari M, Gagliardi M, Fimia GM, Piacentini M. Endoplasmic reticulum stress, unfolded protein response, and cancer cell fate. *Frontiers in oncology*. 2017;7:78.
21. Chevet E, Hetz C, Samali A. Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. *Cancer discovery*. 2015;5(6):586-97.
22. Raven JF, Baltzis D, Wang S, Mounir Z, Papadakis AI, Gao HQ, et al. PKR and PKR-like endoplasmic reticulum kinase induce the proteasome-dependent degradation of cyclin D1 via a mechanism requiring eukaryotic initiation factor 2 α phosphorylation. *Journal of Biological Chemistry*. 2008;283(6):3097-108.
23. Molina-Ruiz FJ, González R, Rodríguez-Hernández MA, Navarro-Villarán E, Padillo FJ, Muntané J. Antitumoral activity of Sorafenib in hepatocellular Carcinoma: effects on cell survival and death pathways, cell metabolism reprogramming, and on nitrosative and oxidative str. *Critical Reviews™ in Oncogenesis*.
24. McQuiston A, Diehl JA. Recent insights into PERK-dependent signaling from the stressed endoplasmic reticulum. *F1000Research*. 2017;6.
25. Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, et al. IRE1 signaling affects cell fate during the unfolded protein response. *science*. 2007;318(5852):944-9.
26. Lin JH, Li H, Zhang Y, Ron D, Walter P. Divergent effects of PERK and IRE1 signaling on cell viability. *PLoS one*. 2009;4(1):e4170.
27. Rahmati M, Amanpour S, Kharman-Biz A, Moosavi MA. Endoplasmic Reticulum Stress as a Therapeutic Target in Cancer: A mini review. *Basic & Clinical Cancer Research*. 2017;9(2):38-48.
28. Drogat B, Auguste P, Nguyen DT, Bouche-careilh M, Pineau R, Nalbantoglu J, et al. IRE1 signaling is essential for ischemia-induced vascular endothelial growth factor-A expression and contributes to angiogenesis and tumor growth in vivo. *Cancer research*. 2007;67(14):6700-7.
29. Maurel M, Chevet E, Tavernier J, Gerlo S. Getting RIDD of RNA: IRE1 in cell fate regulation. *Trends in biochemical sciences*. 2014;39(5):245-54.
30. Agostinis P, Afshin S. Endoplasmic reticulum stress in health and disease: Springer Science & Business Media; 2012.
31. Nadanaka S, Okada T, Yoshida H, Mori K. Role of disulfide bridges formed in the luminal domain of ATF6 in sensing endoplasmic reticulum stress. *Molecular and cellular biology*. 2007;27(3):1027-43.
32. Yuan K, He H-H, Zhang C-Z, Li X-Y, Weng S-P, He J-G, et al. Litopenaeus vannamei activating transcription factor 6 alpha gene involvement in ER-stress response and white spot symptom virus infection. *Fish &*

- shellfish immunology. 2017;70:129-39.
33. Forouhan M, Mori K, Boot-Handford R. Paradoxical roles of ATF6 α and ATF6 β in modulating disease severity caused by mutations in collagen X. *Matrix Biology*. 2018.
 34. Li X, Zhang K, Li Z. Unfolded protein response in cancer: the physician's perspective. *Journal of hematology & oncology*. 2011;4(1):8.
 35. Yorimitsu T, Nair U, Yang Z, Klionsky DJ. ER stress triggers autophagy. *Journal of Biological Chemistry*. 2006.
 36. Gaist D, Andersen L, Hallas J, Sørensen HT, Schrøder H, Friis S. Use of statins and risk of glioma: a nationwide case-control study in Denmark. *British journal of cancer*. 2013;108(3):715.
 37. Yan Y, Xu Z, Dai S, Qian L, Sun L, Gong Z. Targeting autophagy to sensitive glioma to temozolomide treatment. *Journal of experimental & clinical cancer research*. 2016;35(1):23.
 38. Clarke R, Cook KL, Hu R, Facey CO, Tavassoly I, Schwartz JL, et al. Endoplasmic reticulum stress, the unfolded protein response, autophagy, and the integrated regulation of breast cancer cell fate. *Cancer research*. 2012;72(6):1321-31.
 39. Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D. Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. *Nature cell biology*. 2000;2(6):326.
 40. Verfaillie T, Garg AD, Agostinis P. Targeting ER stress induced apoptosis and inflammation in cancer. *Cancer letters*. 2013;332(2):249-64.
 41. Oakes SA, Papa FR. The role of endoplasmic reticulum stress in human pathology. *Annual Review of Pathology: Mechanisms of Disease*. 2015;10:173-94.
 42. Wang Y, Wang JH, Zhang XL, Wang XL, Yang L. Endoplasmic reticulum chaperone glucose-regulated protein 78 in gastric cancer: An emerging biomarker. *Oncology Letters*.
 43. Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. *science*. 2011;334(6059):1081-6.
 44. Corazzari M, Rapino F, Ciccocanti F, Giglio P, Antonioli M, Conti B, et al. Oncogenic BRAF induces chronic ER stress condition resulting in increased basal autophagy and apoptotic resistance of cutaneous melanoma. *Cell death and differentiation*. 2015;22(6):946.
 45. Hill DS, Lovat PE, Haass NK. Induction of endoplasmic reticulum stress as a strategy for melanoma therapy: is there a future? *Melanoma Management*. 2014;1(2):127-37.
 46. Gottesman MM. Mechanisms of cancer drug resistance. *Annual review of medicine*. 2002;53(1):615-27.
 47. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. *Nature Reviews Cancer*. 2013;13(10):714.
 48. Longley D, Johnston P. Molecular mechanisms of drug resistance. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*. 2005;205(2):275-92.
 49. Fu Y, Li J, Lee AS. GRP78/BiP inhibits endoplasmic reticulum BIK and protects human breast cancer cells against estrogen starvation-induced apoptosis. *Cancer research*. 2007;67(8):3734-40.
 50. Hu R, Warri A, Jin L, Zwart A, Riggins RB, Clarke R. NF κ B Signaling is required for XBPI (U and S) Mediated Effects on Antiestrogen Responsiveness and Cell Fate Decisions in Breast Cancer. *Molecular and cellular biology*. 2014;MCB. 00847-14.
 51. Yeung B, Kwan B, He Q, Lee A, Liu J, Wong A. Glucose-regulated protein 78 as a novel effector of BRCA1 for inhibiting stress-induced apoptosis. *Oncogene*. 2008;27(53):6782.
 52. Fujimoto A, Kawana K, Taguchi A, Adachi K, Sato M, Nakamura H, et al. Inhibition of endoplasmic reticulum (ER) stress sensors sensitizes cancer stem-like cells to ER stress-mediated apoptosis. *Oncotarget*. 2016;7(32):51854.
 53. Ranganathan AC, Adam AP, Zhang L, Aguirre-Ghiso JA. Tumor cell dormancy induced by p38SAPK and ER-stress signaling: an adaptive advantage for metastatic cells? *Cancer biology & therapy*. 2006;5(7):729-35.
 54. Pi L, Li X, Song Q, Shen Y, Lu X, Di B. Knockdown of glucose-regulated protein 78 abrogates chemoresistance of hypopharyngeal carcinoma cells to cisplatin induced by unfolded protein in response to severe hypoxia. *Oncology Letters*. 2014;7(3):685-92.
 55. Lee AS. GRP78 induction in cancer: therapeutic and prognostic implications. *Cancer research*. 2007;67(8):3496-9.
 56. Visioli F, Wang Y, Alam GN, Ning Y, Rados PV, Nör JE, et al. Glucose-regulated protein 78 (Grp78) confers chemoresistance to tumor endothelial cells under acidic stress. *PLoS one*. 2014;9(6):e101053.
 57. Piton N, Wason J, Colasse É, Cornic M, Lemoine F, Le Pessot F, et al. Endoplasmic reticulum stress, unfolded protein response and development of colon adenocarcinoma. *Virchows Archiv*. 2016;469(2):145-54.
 58. Carson BB, Sciences CUWCGSoM. Perk Dependent Inhibition of Wnt Signaling by the Unfolded Protein Response: Cornell University; 2015.
 59. Fels DR, Koumenis C. The PERK/eIF2 α /ATF4 module of the UPR in hypoxia resistance and tumor growth. *Cancer Biol Ther*. 2006;5(7):723-8.
 60. Xia Z, Wu S, Wei X, Liao Y, Yi P, Liu Y, et al. Hypoxic ER stress suppresses beta-catenin expression and promotes cooperation between the transcription factors XBPI and HIF1 α for cell survival. *The Journal of biological chemistry*. 2019;294(37):13811-21.
 61. Graner AN, Hellwinkel JE, Lencioni AM, Madsen HJ, Harland TA, Marchando P, et al. HSP90 inhibitors in the context of heat shock and the unfolded protein response: effects on a primary canine pulmonary adenocarcinoma cell line. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*. 2017;33(3):303-17.
 62. Gao Y, Wang HY. Casein kinase 2 Is activated and essential for Wnt/beta-catenin signaling. *The Journal of biological chemistry*. 2006;281(27):18394-400.
 63. Cruciat CM. Casein kinase 1 and Wnt/beta-catenin signaling. *Current opinion in cell biology*. 2014;31:46-55.
 64. Manni S, Carrino M, Piazza F. Role of protein kinases CK1 α and CK2 in multiple myeloma: regulation of pivotal survival and stress-managing pathways. *Journal of Hematology & Oncology*. 2017;10(1):157.
 65. Hosoi T, Korematsu K, Horie N, Suezawa T, Okuma Y, Nomura Y, et al. Inhibition of casein kinase 2 modulates XBPI-GRP78 arm of unfolded protein responses in cultured glial cells. *PLoS One*. 2012;7(6):e40144.
 66. Manni S, Brancalion A, Tubi LQ, Colpo A, Pavan L, Cabrelle A, et al. Protein kinase CK2 protects multiple myeloma cells from ER stress-induced apoptosis and from the cytotoxic effect of HSP90 inhibition through regulation of the unfolded protein response. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2012;18(7):1888-900.
 67. Hetz C, Chevet E, Oakes SA. Proteostasis control by the unfolded protein response. *Nat Cell Biol*. 2015;17(7):829-38.